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EXAMINER
SACKEY, EBENEZER O

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,361	Applicant(s) HEATON ET AL.
	Examiner EBENEZER SACKEY	Art Unit 1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/17/03 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 12 - 20 is/are pending in the application.

4a) Of the above, claim(s) 16, 18 - 20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 12-15 and 17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 12-22 are pending.

Receipt of the Priority Documents, Information Disclosure Statement and Preliminary amendment filed on 02/03/02 and 07/08/02 respectively is acknowledged and has been entered into the file. The signed 1449 is attached herewith.

Response to Restriction

Applicant's election without traverse of Group I, species of Example 1 in Paper No.10 is acknowledged. Claim 13 has been rejoined with Group I.

The following generic concept as depicted in claims 12 and 13, formulae (I) and (II) is identified for examination along with the elected embodiment: A and B are taken together to form a benzopyran ring with formulae (I) or (II) wherein, Z is H and Z_A is Cl; R_1 and R_2 is H, alkyl, OH and $OCOR_{10}$; W is H, OH, $OCOR_{10}$; R_6 is H, alkyl, OH; R_{14}-R_{16} is H. The remaining subject matter of claims 12, 13, 14 and 17 (in part) in their entirety

stands withdrawn from further consideration under 37 CFR 1.142(b) as constituting other patentably distinct inventions.

The withdrawn subject matter of claims 12, 13, 14 and 17 (in part) in their entirety is properly restricted as said subject matter differs in structure and element from the elected subject matter so as to be patentably distinct therefrom, i.e. a reference anticipating the elected subject matter would not even render obvious the withdrawn subject matter and fields of search are not co-extensive.

Claim Rejections - 35 U.S.C. § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of the compounds and the binding affinity for both subtypes of estrogen receptor (example 16), does not reasonably provide enablement for the "prevention/treatment of all

the diseases listed" because applicants have not shown that there is a correlation between the binding activity and all the listed diseases/disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following phrases are not properly supported in the specification: In claim 15, for example "prevention of menopausal syndrome", page 11, line 2; "all forms of cancer", page 11, line 6; "diseases associated with oxidant stress", page 11, lines 11-12 of the preliminary amendment filed on 07/08/02. The specification fails to adequately teach how to use the invention properly by failing to provide an enabling disclosure regarding the above phrases. Because of the high level of unpredictability associated with chemical or biological systems, a greater amount of evidentiary support is needed in order to fully satisfy the requirement of 35 U.S.C. 112, first paragraph, that applicants provide sufficient guidance as regards "how to use" the invention. For example what is encompassed by "diseases associated with oxidant stress" or "prevention of menopausal syndrome" or

"all forms of cancer". These phrases consists a plethora of diseases. The specification has shown that the testing protocol used is accepted in the art as being predictive of the utility alleged. In vitro tests or tests using animal models, by themselves, do not establish the usefulness of an invention absent art-recognized correlation between such tests and the ultimate use. Merely identifying substances as objects for further use-testing (speculative utility) is insufficient to provide an enabling disclosure. See Brenner V. Manson, 148 USPQ 689 or In re Kirk, 153 USPQ 48. Additionally, the claim lists diseases such as Reynaud's disease, Reynaud's phenomenon, Buerger's disease etc. As defined, the claim embraces diseases which is broader than the enabling disclosure. It is not believable on its face in view of the contemporary knowledge of the art that one or more related compounds would have the capacity to treat an extraordinary amount of unrelated diseases which require different pathways and mechanisms.

Applicants need to point out in the specification where there is support including pharmacological data for the above phrases. A mere statement does not provide enabling support for such a utility.

Inventions targeted for human therapy bear a particular heavy responsibility to provide supporting data because of the unpredictability in biological responses to therapeutic treatment. Also, the standard of enablement is higher of such inventions simply because effective treatments for disease conditions are relatively rare, and may be prima facie unbelievable in the absence of strong supporting data. See Ex Parte Stevens, in which a prima facie case of nonenablement against a method of treating cancer was affirmed based solely on legal precedents. Ex Parte Stevens, 16 USPQ 2nd 1379 (B.P.A.I. 1990). See also Ex Parte Chwang, 231 USPQ 751 (B.P.A.I 1986) and Ex Parte Krepelka, 231 USPQ 746 (B.P.A.I. 1986).

In the instant application, the specification is not enabling for the broad class of prevention or cancers encompassed by the invention because the limited in vivo data does not support all forms of cancer or the prevention of any disease. In view of this art's unpredictability, and the fact that no clinically effective preventions are known, a conclusion of this activity cannot be reached without data for the entire scope of the invention.

Of course, the inclusion of some inoperative embodiments in a generic claim is not enough in itself to render the claim unpatentable. However, when the number of inoperative embodiments becomes significant, or when the likelihood is high that a significant number of the embodiments are inoperative, one of ordinary skill must resort to undue experimentation to practice the claimed invention, and at this point the generic may properly be found to be unpatentable. See Atlas Powder Co. V. E.I. Dupont de Nemours, 750 F .2d 1569, 1576 (Fed. Cir. 1984).

"In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty in their performance characteristics predicted by resort to know scientific law. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of factors involved". Amgen, Inc. v. Chugai Pharmaceutical Co. Lts., 13 USPQ .2d 1737, 1775 (1980), citing In re Fisher, 527 F .2d 833, 839 (CCPA 1970).

The Amgen decision, Id. At 1776, went on to point out that, while 50 to 80 analogs had been tested in vitro and exhibited activity varying over several orders of magnitude, this was not sufficient to conclude that the same analogs would have comparable biological activity. The case of non-enablement was therefore found to be even stronger against the remaining analogs encompassed by the implicated claim, for which in vitro data had been furnished. After extensive testimony, the claim was held invalid for the failure to satisfy the enablement requirement of sec. 112.

The present rejection is believed to be consistent with the aforementioned decisions, as well as the decision in In re Marzocchi, 169 USPQ 367, 369 (1971) in which the court stated that:

"As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements

contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proof indicating that the teaching contained in the specification is truly enabling". The specification does not provide sufficient teaching commensurate with the scope of the claim.

Claim Rejections - 35 U.S.C. § 112

2.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recite the word "comprise", claim 12, page 2, the last line and in all occurrences. "Comprise" is an opened-ended word which permits the

inclusion of unrecited elements. It is suggested that "comprise" be replaced with --consist--.

It is also suggested that for clarity of the claims, the word "including" in all occurrences be deleted from the claims.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a

nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 15 and 17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8 and 9 of U.S. Patent No. 6,340,703. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is considerable overlap between the claims of the instant application and claims of '703'. The claims of '703' relate to a method for the treatment or prevention of osteoporosis, said method comprising the administration of compounds and compositions of formononetin, whereas the instant claims are drawn to for example methods of treating or prevention of osteoporosis with compounds or analogue of formula (I) or (II). Formononetin is a

subgenus of formula (I) which has been shown to posses pharmaceutical activities as disclosed by '703'.

The instant method and compositions would have been obvious from the reference teaching in the absence of any unobvious or unexpected properties or results especially since one of ordinary skill in the art would expect that compounds closely related structurally would have similar properties.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 12, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kristiina Wahala et al. "Synthesis and Labeling of Isoflavone

Phytoestrogens, Including Daidzein and Genistein", Proceedings of the Society for Experimental Biology and Medicine, (1995), 208(1), pages 27-32. Applicants claim an Isoflavone compound or analogue of formula (I), wherein the substituents are as defined. Kristiina Wahala et al. discloses identical Isoflavone compounds. See the entire publication, especially page 29 wherein an Isoflavone compound is depicted in which R is H.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 12-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorbach (U.S.Patent Number 5,733,926).

Applicants claim an Isoflavone compounds or analogue of formula (I) and (II) wherein the substituents are as defined, composition and method of using said compounds.

Determination of the scope and content of the prior art (M.P.E.P.. §2141.01)

Gorbach discloses for a similar purpose compounds and compositions (formononetin, daidzein) which generically corresponds to the claimed compounds and composition as note the abstract, column 1, lines 42-47 and lines 58-60. The said compounds and compositions are under the genus of formulae (I) and (II). Additionally, see column 2, lines 24-27. Furthermore, the reference discloses a method for treating for example Alzheimer with compounds or compositions of formulae (I) or (II). See column 1, line 35. See when A and B are taken together to form a

benzopyran ring with formulae (I) or (II), in which R_1 and Y are both OH, and each of W, Z and R_2 are all hydrogen.

Ascertainment of the difference between the prior art and the claims (M.P.E.P.. §2141.02)

The instant compounds differs from Gorbach in the generic description of the compounds. Gorbach discloses for example formononetin, whereas the instant claims are drawn compounds or analogue of formula (I) or (II). Formononetin is a subgenus of formula (I) which has been shown to posses pharmaceutical activities. See when A and B are taken together to form a benzopyran ring with formula (I), in which R_1 and Y are both OH, and each of W, Z and R_2 are all hydrogen.

Finding of prima facie obviousness---rational and motivation (M.P.E.P.. §2142-2143)

One of ordinary skill in the art would be motivated to prepare compounds so closely related to be homologous, isomeric or structural analogs of compounds of the reference so as to be structurally obvious therefrom, or would be rendered obvious by the teachings of the reference in the absence of any unobvious properties especially since one of ordinary

skill would expect compounds so closely related structurally to have similar properties. Furthermore, one of ordinary skill would be motivated to use the teachings of Gorbach to prepare compounds and compositions in the expectation that all compounds and compositions under the genus would be useful for the reference purpose, such as treating various disease state.

Thus, the instantly claimed compounds, compositions and methods of use would have been suggested to one of ordinary skill.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Sackey whose telephone number is (703) 305-6889. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (703) 308-4537. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

EOS

May 5, 2003

Joseph K. McKane

Supervisory Patent Examiner

Art Unit 1626, Group 1600

Technology Center 1

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